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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/051,013	10/09/1998	TIMOTHY H. BESTOR	48075-B-PCT	7512

7590 12/10/2003

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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 12/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/051,013	BESTOR, TIMOTHY H.	
	Examiner	Art Unit	
	David J Steadman	1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *19 November 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): see attachment.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attachment*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-8,10-15,18,24-26 and 42-46*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *Notice of References Cited*

ADVISORY ACTION

[1] Claims 1-8, 10-15, 18, 24-26, and 42-46 are pending in the application.

[2] Claims 1-8, 10-15, 18, 24-26, and 42-46 are rejected.

[3] Applicant's amendment to the claims filed November 19, 2003 is acknowledged. This listing of the claims replaces all prior versions of the claims.

[4] The request for reconsideration is acknowledged, however the amendment does not place the application in condition for allowance for the reasons stated below.

[5] In view of applicant's cancellation of claim 9, the rejections under 35 USC 112, second paragraph and 35 USC 112, first paragraph, are withdrawn.

[6] The written description rejection of claims 1-8, 10-15, 18, 24-26, and 42-46 under 35 USC 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in previous Office actions. Applicant maintains the position that the specification adequately describes the genus of recited chimeric proteins. Applicant presents the following arguments in support of this position: 1) the specification discloses a representative number of chimeric proteins; 2) no structure/function relationship need be established nor is a chemical structure required for adequate description; and 3) the text of *UC California v Eli Lilly* as quoted by the examiner is inapplicable to the instant rejection. Applicant's argument is not found persuasive.

The examiner maintains his position that the specification fails to describe a representative number of species of the recited genus of chimeric proteins. For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed

genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a "representative number of species" means that the species which are adequately described are representative of the entire genus. The genus of recited chimeric proteins encompasses species comprising a DNA methyltransferase having attenuated DNA binding activity and a DNA binding protein that binds to a gene's promoter. The recited genus of DNA methyltransferases encompasses species having widely variant structures - including mutant DNA methyltransferases having the recited attenuated DNA binding activity. Also, the species of DNA binding proteins encompasses species having widely variant structures and functions – including those structures of naturally-occurring and non-naturally occurring DNA binding proteins having the ability to bind a promoter of any given gene. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the two prophetic representative examples fail to represent the entire genus of recited chimeric proteins, which encompasses species having widely variant structures and/or functions as described above.

Regarding applicant's assertion that a structure/function relationship is not required to adequately describe the invention and the text of *UC California v Eli Lilly* quoted by the examiner is inapplicable to the instant rejection, it is noted that structures of the components of the chimeric protein are an essential feature of the claimed invention and should therefore have adequate description in the specification, which they do not. In fact, the revised interim guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, state that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. The examiner acknowledges that only a representative number of species of the genus of recited chimeric proteins or encoding nucleic acids is necessary to satisfy the written description requirement. However, the specification fails to provide such a representative number of species, particularly the structures of such species.

[7] The scope of enablement rejection of claims 1-8, 10-15, 18, 24-26, and 42-46 under 35 USC 112, first paragraph, is maintained for the reasons of record and the reasons stated below. The rejection was fully explained in previous Office actions. Applicant argues the specification fully enables the claimed invention and presents the

following arguments in support thereof: 1) the breadth of the claims is relatively narrow and is not broad as argued by the examiner; 2) the specification provides adequate guidance; 3) the ability to isolate proteins or encoding nucleic acids with altered functionality is not highly unpredictable; and 4) the examiner provides no evidence that the claimed pharmaceutical composition of claims 44-46 would not be effective in treating a disease. Applicant's arguments are not found persuasive.

Addressing argument 1), it is the examiner's position that the specification fails to enable the broad scope of the claimed invention. For example, claim 1 encompasses a chimeric protein comprising two component proteins for inhibiting gene expression by methylation of a methylation site within a promoter. The first component being any DNA methyltransferase having any variation resulting in attenuated DNA binding activity while maintaining methyltransferase activity and the second component being any DNA binding protein that binds to any gene's promoter - including promoters yet to be identified. The entire scope of the claims is, contrary to applicant's assertion, not narrow, but is overly broad in scope and is NOT enabled by the instant specification.

Addressing argument 2), the specification fails to provide the necessary guidance for making the claimed invention. The working examples provided by the specification are mostly prophetic and fail to provide even a single specific mutation in a DNA methyltransferase that would result in attenuated DNA binding while maintaining methyltransferase activity. Furthermore the specification fails to provide guidance regarding DNA binding proteins that would bind to a specific DNA promoter sequence. A skilled artisan recognizes that the structure of a DNA binding protein will determine its

ability to bind a specific promoter sequence and guidance is therefore required to direct a skilled artisan to those promoters that will bind a given promoter sequence. Such guidance has not been provided.

Addressing argument 3), due to the broad scope of the claims and the lack of guidance and working examples provided in the specification, there exists a high degree of unpredictability for making the entire scope of the claimed invention. It is noted that applicant states that one cannot predict which mutations will result in the desired reduction in DNA binding affinity of a DNA methyltransferase (page 40, lines 10-11). While this statement was allegedly provided as a prelude to the necessity of using random mutagenesis, it nonetheless provides evidence of the unpredictability for generating the desired DNA methyltransferase variants. Furthermore, a skilled artisan would recognize that this unpredictability is compounded by the necessity for not only generating a variant DNA methyltransferase with attenuated DNA binding activity, but also having maintained the ability to methylate DNA as is required to inhibit gene expression. While random mutagenesis is used widely in the art, a skilled artisan would have no way of predicting whether the use of this method as applied to any DNA methyltransferase to generate a variant with attenuated DNA binding activity with the ability to methylate DNA would be successful. As the name indicates - it is random and not specific and so a skilled artisan would recognize the high degree of unpredictability in obtaining the desired variant. Furthermore, as this method is completely random, a large amount of experimentation may be necessary to obtain - if at all possible - the desired mutant, as acknowledged by applicant (page 42, lines 4-7). Since this method is

completely random and applicant has provided no specific mutations that will guide a skilled artisan for making the desired variant, a skilled artisan would recognize the large amount of experimentation required to make the invention. In addition to the statement provided in the specification acknowledging the high degree of unpredictability in mutating an encoding nucleic acid with an expectation of obtaining a protein having the desired activity, the prior art further acknowledges such. For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability... ...they also serve to emphasize how difficult it is to design *de novo* stable proteins with specific functions" (page 247).

Addressing argument 4), it is noted that there is no evidence of record that the claimed pharmaceutical composition can be used to successfully treat, prevent, or ameliorate any disease condition. Thus, it is highly unpredictable as to what diseases can be effectively treated using the claimed pharmaceutical composition. As stated in a previous Office action, the art clearly supports the high degree of unpredictability in using the claimed pharmaceutical composition to treat a disease. Neither the specification nor the prior art provide sufficient guidance as to what specific diseases could be successfully treated by administering a pharmaceutical composition comprising said vector, and attempting to identify a disease treatable using said pharmaceutical composition would constitute undue experimentation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (703) 746-5078. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652